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Endothelial cells as a target to modulate thrombosis

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Endothelial cells may play a role during venous thrombus resolution, as suggested by findings in mice. Furthermore, defective angiogenesis and impaired thrombus revascularization may underlie the accumulation of thrombofibrotic material, which is observed in patients with Chronic Thromboembolic Pulmonary Hypertension (CTEPH). In our work using diverse primary endothelial cells in culture, endothelial-specific transgenic mice (i.e. with endothelial-specific deletion of p53 or TGFßRII) subjected to inferior Vena cava ligation and pulmonary endarterectomy (PEA) specimens from CTEPH patients we try to better understand the role of endothelial cells during thrombus resolution.

Our findings suggest that p53 accumulation and heparanase overexpression in senescent endothelial cells are critically involved in mediating the increased risk of venous thrombosis with age. On the other hand, TGFß signaling in endothelial cells contributes to non-functional neovessel formation and chronic thromboembolic remodeling, such as seen in CTEPH patients.

Curriculum Vitae

Dr Magdalena Bochenek

Educational training

2003 – 2005	Master of Biotechnology, "Medical Biotechnology", University of Wroclaw, Poland; grade 1; Master thesis prepared at the University of Reims, France, laboratory of Medical Biochemistry during the final year of my thesis project (2005, semester IIIIV)
2000 – 2003	Bachelor of Biology, "Microbiology", University of Opole, Poland; grade 1

Doctoral thesis (Doctor of Philosophy)

22 January 2009 PhD thesis "Regulation of cell motility by ephrin-B2 signaling"; laboratory of Prof. Catherine Nobes, Department of Physiology and Pharmacology, School of Medical Sciences, University of Bristol, Bristol, UK

Professional experience

since November 2013	Postdoctoral research associate with Prof. Katrin Schäfer, Center for Thrombosis and Hemostasis (CTH) and Center for Cardiology, Cardiology I, University Medical Center Mainz, Germany
January – October 2013	Postdoctoral research associate with Prof. Mirko HH Schmidt, Department of Microanatomy and Neurobiology, University Medical Center Mainz, Germany
November 2008 – 2012	Postdoctoral research associate with Prof. Ralf H. Adams, Department of Tissue Morphogenesis, Max-Planck-Institute for Molecular Biomedicine, Muenster, Germany

Awards and grants

2018	Translational Research Project entitled: "Importance of endothelial protein C receptor expression for new vessel formation in response to ischemia" (start: 01.02.2019)
2018	Deutsches Zentrum für Herz-Kreislaufforschung e.V.; applicant for cooperation with Shared Expertise SE-030 (Zebrafish-Platform) (start: 01.01.2019)
2017	Translational Research Project entitled "Endothelial cells as a modulator of thrombus formation and thrombus non-resolution in Chronic Thromboembolic Pulmonary Hypertension"
2017	Intramural Research Funding (Stufe 1) proposal entitled „Role of thrombomodulin signaling during new vessel formation following ischemia" (start: 01.01.2017)

2017	Deutsches Zentrum für Herz-Kreislaufforschung e.V.; co-applicant for cooperation with Shared Expertise SE-105 (Athero-LCM)
2015	Poster Price at the 2nd European Spring School Greece for the poster: "Comparative Analysis of Vascular Remodeling Processes in Endarterectomy Specimens of Patients with CTEPH and in Murine Venous Thrombi"
2014	Initiation of Platform 8 (Vascular Remodeling; start March 2014) and Platform Supervision
2014	Virchow fellowship funded by Bundesministerium für Bildung und Forschung (BMBF; start 01.05.2014)
2008	University of Bristol; travel stipend to attend Keystone Conference
2005 – 2008	University of Bristol; PhD scholarship
2004 – 2005	Socrates/ Erasmus Program; Master Degree scholar

Selected publications:

1. Brandt M, Giokoglu E, Garlapati V, Bochenek ML, Molitor M, Hobohm L, Schönfelder T, Münzel T, Kossmann S, Karbach SH, Schäfer K, Wenzel P. Pulmonary arterial hypertension and endothelial dysfunction is linked to NADPH Oxidase-derived superoxide formation in venous thrombosis and pulmonary embolism in mice. Oxidative Med and Cell Longevity (2018) doi: 10.1155/2018/1860513.
2. Bochenek ML*, Bauer T*, Gogiraju R,Nadir Y,Mann A,Schönfelder T, Hünig L, Brenner B,4 Münzel T, Wenzel P, Konstantinides S, Schäfer K. Endothelial tumor suppressor p53 is essential for venous thrombus formation in aged mice. Blood Adv (2018) Jun 12;2(11):1300-1314. doi: 10.1182/bloodadvances.2017014050.
3. Jäger M*, Hubert A*, Gogiraju R, Bochenek ML, Münzel T, Schäfer K. Endothelial Protein Tyrosine Phosphatase-1B knockdown enhances neointima formation in mice with diet-induced obesity. Antioxidants and Redox Signaling. (2018) Feb 1. doi: 10.1089/ars.2017.7169.
4. Hubert A, Bochenek ML, Schütz E, Gogiraju R, Münzel T, Schäfer K. Selective Deletion of Leptin Signaling in Endothelial Cells Enhances Neointima Formation and Phenocopies the Vascular Effects of Diet-Induced Obesity in Mice. Arterioscler Thromb Vasc Biol. (2017) Jul 13. pii: ATVBAHA.117.309798. doi: 10.1161/ATVBAHA.117.309798.
5. Chrysanthopoulou A, Kambas K, Stakos D, Mitroulis I, Mitsios A, Vidali V, Angelidou I, Bochenek ML, Arelaki S, Arampatzioglou A, Skendros P, Konstantinides S, Andreakos E, Schäfer K, Ritis K. Inorganic polyphosphate and Interferon lambda1/IL-29 are novel partners in the regulation of neutrophil-driven thromboinflammation. J Pathol (2017) Sep;243(1):111-122. doi: 10.1002/path.4935.
6. Schütz E, Bochenek ML, Riehl DR, Bosmann M, Münzel T, Konstantinides S, Schäfer K. Absence of Transforming Growth Factor beta 1 in Murine Platelets Reduces Neointima Formation without Affecting Thrombosis. Thromb Haemost (2017) Jul 20;117(9). doi: 10.1160/TH17-02-0112).
7. Bochenek ML, Rosinus NS, Lankeit M, Hobohm L, Bremmer F, Schuetz E, Klok FA, Horke S, Wiedenroth CB, Münzel T, Lang IM, Mayer E, Konstantinides S, Schäfer K.

From thrombosis to fibrosis in Chronic Thromboembolic Pulmonary Hypertension. Thromb Haemost (2017) Apr 3;117 (4):769-783. doi:10.1160/TH16-10-0790.

8. Bochenek ML, Schütz E, Schäfer K. Endothelial cell senescence and thrombosis; Ageing clots. Thromb Res (2016) 147:36-45. doi: 10.1016/j.thromres.2016.09.019. (invited review).
9. Gogiraju R, Schroeter MR, Bochenek ML, Hubert A, Münzel T, Hasenfuss G, Schäfer K. Endothelial deletion of protein tyrosine phosphatase-1B protect against pressure overload-induced heart failure in mice. Cardiovasc Res (2016) 111:204-216. doi: 10.1093/cvr/cvw101.
10. Shah B, Lutter D, Bochenek ML, Kato K, Tsytsyura Y, Glyvuk N, Sakakibara A, Klingauf J, Adams RH, Püschel AW. C3G/Rapgef1 is required in multipolar neurons for the transition to a bipolar morphology during cortical development. PloS One (2016) 11: e0154174. doi: 10.1371/journal.pone.0154174.
11. Gogiraju R, Xu X, Bochenek ML, Steinbrecher JH, Lehnart SE, Wenzel P, Kessel M, Zeisberg EM, Dobbelstein M, Schäfer K. Endothelial p53 deletion improves angiogenesis and prevents cardiac fibrosis and heart failure induced by pressure overload in mice. J Am Heart Assoc (2015) 4. pii: e001770. doi: 10.1161/JAHA.115.001770.